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CORRESPONDENCE

Letters to the Editor

The CAPRIE-Like Subgroups of CHARISMA: A CAPRIEciously Biased Analysis of an unCHARISMAtic Truth

In a textbook example of an improper subgroup analysis (1) (one defined by events subsequent to randomization, in this case fabricating new "CAPRIE [Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events]-like" inclusion criteria), Bhatt et al. (2) present data suggesting that persons with a prior history of stroke, myocardial infarction (MI), or peripheral vascular disease (PVD) may benefit from long-term dual antiplatelet therapy with aspirin plus clopidogrel versus aspirin alone. It is illuminating to examine this analysis in the historical and statistical context of the clinical trial evidence from which it was derived.

In the CAPRIE trial (3), a trial twice as large as this "CAPRIE-like" CHARISMA (Clopidogrel for High Atherothrombotic Risk, Ischemic Stabilization, Management, and Avoidance) subgroup, a marginally statistically significant result ($p = 0.043$) was observed for the primary end point, with statistical heterogeneity of treatment effect ($p = 0.042$) being observed between the 3 predefined subgroups of patients with recent stroke, MI, or PVD. Only the PVD subgroup benefited from the use of clopidogrel versus aspirin. Despite statistically stronger evidence of heterogeneity of ($p = 0.042$) than of overall treatment effect ($p = 0.043$), the CAPRIE trial's authors concluded that their hypothesis of universal superiority of clopidogrel over aspirin for all vascular disease was correct anyway and presented in their primary manuscript another improper post hoc subgroup analysis designed to make their data comply with their hypothesis. Specifically, they analyzed patients with newly fabricated inclusion criteria of any prior history of coronary artery disease and, unlike the actual CAPRIE trial MI patient subgroup, showed a statistically significant reduction in recurrent vascular events.

History has now repeated itself. The most statistically significant results presented in the primary CHARISMA trial report (4) were excessive "moderate" bleeding events in the dual-therapy group ($p < 0.001$) and excess cardiovascular mortality in the predefined primary prevention subcohort ($p = 0.01$) treated with dual therapy. The primary end point was negative. Ironically, and perhaps predictably, 10 years after the CAPRIE trial, the CHARISMA trial's authors have suddenly selectively embraced the value of heterogeneity of treatment effect (between the primary and secondary prevention subcohorts) statistically evident in the CHARISMA trial ($p = 0.045$), using it as a philosophical springboard to manipulate the data of the CHARISMA trial to fit their hypothesis of the universal superiority of clopidogrel (this time when combined with aspirin) over aspirin via the currently published analysis.

Positive subgroups within negative trials such as the CHARISMA trial are virtually always the result of confounding or bias, especially post hoc defined subgroups. How many additional unpublished subgroup analyses of the CHARISMA trial have been performed? Are we to ignore the results of the MATCH (Management of Atherothrombosis With Clopidogrel in High-Risk Patients) trial (5), which showed statistically significant net harm for patients with recent stroke/transient ischemic attack (TIA) treated with clopidogrel plus aspirin versus clopidogrel alone, in favor of those of an improper post hoc subgroup analysis with less than one-half of the analogous patient population? No clinical trial has ever shown superiority of clopidogrel, plus or minus aspirin, over aspirin or clopidogrel alone for preventing recurrent vascular events in patients with recent or remote history of stroke/TIA.

If a randomized trial of aspirin plus clopidogrel versus aspirin alone in a population of patients with any prior history of stroke, MI, and/or PVD is performed, I predict it will show no statistically significant net benefit.

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Reply

Dr. Gebel takes issue with our recent subgroup analysis of the CHARISMA (Clopidogrel for High Atherothrombotic Risk, Ischemic Stabilization, Management, and Avoidance) study, which he labels improper because he incorrectly believes it was defined by events that occurred after randomization (1,2). In fact, the subgroup consisted of patients with documented ischemic